Body Fat Is the Main Predictor of Fibrinogen Levels in Healthy Non-obese Men

Mario Bo, Silvio Raspo, Fabio Morra, Maurizio Cassader, Giancarlo Isaia, and Leone Poli

Previous studies have demonstrated that circulating levels of C-reactive protein (CRP), a marker of cardiovascular risk, are strictly related to body fatness. Elevated fibrinogen levels are also predictive of future cardiovascular events. The metabolic background of this relationship and the predictors of fibrinogen levels have not been well established. We aimed to evaluate whether fibrinogen levels are associated with body fat content and distribution and to determine the independent predictors of fibrinogen levels in a sample of healthy, non-obese, nonsmoking young adult men. Age, anthropometric measures (body mass index [BMI], waist-to-hip ratio [WHR]), total and regional fat content (determined by dual x-ray absorptiometry [DXA]), metabolic variables (total cholesterol [T-Chol], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]; triglycerides [TG]; glucose and insulin levels; fasting insulin resistance index [FIRI]; blood pressure), interleukin-6 (IL-6), and acute-phase reactants levels (fibrinogen, highly sensitive [hs]-CRP) were determined in 87 healthy nonsmoking, non-obese subjects. Linear regression analysis was used to evaluate the association between body fat, fibrinogen, and metabolic variables, and multiple regression model analysis was used to examine the independent predictors of fibrinogen levels. Eighty-seven (30.5 ± 3.5 years) non-obese (mean BMI 24.1 ± 3.5) men were studied. Fibrinogen levels were strongly associated with measures of body fat and with metabolic variables. Total body fat ($P < .0001$) and LDL-cholesterol ($P < .01$) were the independent predictors of fibrinogen levels, accounting for 29.5% and 10.9% of its variance, respectively. Total body fat was the best independent predictor of hs-CRP levels, accounting for 32.5 % of its variance. We conclude that in healthy, non-obese subjects, body fat content is the main predictor of fibrinogen levels, as well of hs-CRP levels. These findings support the speculation that there is a direct mechanism by which adipose tissue might regulate the levels of circulating acute-phase reactants.

ELEVATED LEVELS of several inflammatory mediators among apparently healthy subjects have proven to have predictive value for future vascular events.[1-8] For clinical purposes, highly sensitive C-reactive protein (hs-CRP) appears to be the most promising inflammatory biomarker, by reason of its longer half-life, without relevant circadian variation, and its easy determination by commercially available standardized high-sensitivity assays.[9-11] However, for many years, fibrinogen has been recognized as an important risk factor for cardiovascular events and several prospective epidemiological studies have documented an association between fibrinogen and future cardiovascular diseases, which is not substantially modified after multivariate adjustment for other risk factors.[12-15] The metabolic background of this strong relationship between fibrinogen levels and cardiovascular risk has not been fully elucidated, although a number of studies showed significant associations between fibrinogen and several other cardiovascular and hemostatic variables.[16-23] Unfortunately, measurements for fibrinogen were poorly standardized for some time, thereby limiting its wide adoption in the clinical setting. Currently accepted assays for fibrinogen are widely available and have acceptable coefficients of variation.[24,25] For these reasons, fibrinogen is currently one of the few acute-phase reactants that might be considered as predictor of cardiovascular risk.[24] However, most of the research in recent years has been focused on hs-CRP levels, and fibrinogen has not been as extensively investigated. It has been clearly shown that levels of hs-CRP are increased in overweight/obese subjects,[26-31] in patients with the metabolic syndrome (MS),[32,33] and in the presence of diabetes and insulin resistance.[28,31-36] Central adiposity is a common feature in these conditions: it may accentuate the degree of insulin resistance, which in turn greatly increases the likelihood of developing the cluster of metabolic alterations described as MS.[37] Although the nature of the relation between hs-CRP and adiposity has not been fully elucidated, it has been suggested that adipose tissue acts as a source of circulating interleukin-6 (IL-6), the main cytokine regulating the synthesis of hs-CRP by the liver.[26,28,38] Previous studies showed that also fibrinogen expression on the transcriptional level may be regulated by IL-6.[39-41] Moreover, increased levels of fibrinogen have been observed in obese subjects.[15,18,22] Therefore it should be expected that also fibrinogen levels are strictly related to body fatness.[42] However, to the best of our knowledge, the potential associations between fibrinogen and total and regional body fat composition have never been investigated in healthy non-obese men. We hypothesized that in healthy non-obese subjects body fat may be the main predictor of fibrinogen concentrations, as well of hs-CRP levels.

In the present study on healthy, young adult non-obese subjects, we aimed to evaluate, first, whether fibrinogen values correlate with body fat content and distribution (determined using dual-energy x-ray absorptiometry [DXA]) and, second, whether body fat is an independent predictor of fibrinogen, as well of hs-CRP levels.

MATERIALS AND METHODS

The study was conducted at the Lipid Clinic of the Department of Geriatrics of a University teaching hospital in Turin, Italy. Participants were recruited through inside advertisement among the young adult (age 20 to 40 years) men of the hospital staff. Among those who were

From Azienda Ospedaliera San Giovanni Battista, Department of Medical and Surgical Disciplines, Section of Geriatrics, University of Turin, Turin, Italy.

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Address reprint requests to Mario Bo, MD, Azienda Sanitaria Ospedaliera San Giovanni Battista Torino, Divisione di Geriatria e Gerontologia, C.so Bramante 88, 10126 Torino, Italy.

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apparently healthy and free from history or evidence of inflammatory diseases, volunteers were enrolled after they provided written informed consent.

In all subjects, a careful medical history was collected and information was obtained on smoking habits and drug consumption. Smokers, obese subjects (body mass index [BMI] $>$ 30 kg/m^2) and patients with diabetes were excluded. Subjects with history or evidence on physical examination of cardiovascular disease, peripheral vascular disease, or stroke were excluded. A standard 12-lead electrocardiogram (ECG) was performed in each patient; subjects with major ECG abnormalities (Q-waves, ST-segment depression, left bundle branch block, or T-wave inversion) were excluded. Subjects using aspirin, other anti-inflammatory drugs, or drugs known to affect insulin and glucose levels or hs-CRP and plasma lipoproteins levels were excluded. All subjects were not allowed to take any medication for at least 24 hours before investigation.

Height (meters), weight (kilograms), and waist and hip circumferences (centimeters) were measured. BMI and the waist-to-hip ratio (WHR) were calculated. Blood pressure (BP) was assessed with a standard mercury sphygmomanometer, after a 5-minute rest in the supine position; BP was measured 3 times at the right upper arm with an appropriately sized cuff and the mean value was used in the analyses. Normal BP values were defined according to those adopted for the definition of the MS.[37]

Total and regional body composition was determined by DXA, using a fan beam Hologic QDR 4500 A absorptiometer (Hologic Europe, Zaventem, Belgium).[43,44] Total and regional (trunk, arms, and legs) body composition was evaluated to assess absolute (grams) and percent fat mass (FM). For the estimation of precision, duplicate scans were obtained on the same day for 10 patients. The correlations between duplicate scans ranged from 0.898 and 0.997, and the coefficient of variation for FM was 1.1%.

Blood samples were collected from an antecubital vein into vacutainer tubes containing EDTA after a 12-hour overnight fast for the measurement of plasma lipid and lipoprotein levels. Total cholesterol (T-Chol) and triglycerides (TG) were measured using standard commercial enzymatic kits (CHOD-PAP and GPO-PAP methods, Roche Diagnostics, Mannheim, Germany). HDL-cholesterol (HDL-C) levels were measured trough enzymatic colorimetric assay by a direct method (ADVIA 1650/2400, Bayer, Milano, Italy) after separation of cholesterol from non-HDL particles. LDL-cholesterol (LDL-C) concentration was calculated according to the Friedewald formula.[45] Plasma fibrinogen was quantified automatically through functional coagulative assay according to the Clauss method (STA-Fibrinogen, Roche). Pentameric CRP levels were measured with a highly sensitive immunoassay that used a monoclonal antibody coated with polistirene particles (hs-CRP); the assay was performed using a Behring BN-100 nephelometer (DADE Behring, Marburg, Germany) according to the method described by the manufacturer.[46-48] IL-6 was measured by quantitative sandwich enzyme immunoassay technique (R&D Systems, Minneapolis, MN).[49,50] Glucose was enzymatically determined by the hexokinase method. Serum insulin was determined by monoclonal antibody method (Insulin IRMA CT, RADIM, Pomezia, Italy). Insulin resistance was calculated through the fasting insulin resistance index (FIRI): fasting glucose (mmol/L) $\times$ fasting insulin (mU/L)/25.[51]

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects.

The distribution of continuous variables was evaluated by graphical method (skewness and kurtosis) and by Kolmogorov-Smirnov test; the skewed variables were log-transformed for all the analyses. Linear regression analysis was used to evaluate univariate association between acute-phase reactants (fibrinogen and hs-CRP), body fat, and metabolic variables. The significant associations were entered into a multiple regression model to examine the independent predictors of fibrinogen and hs-CRP levels. A probability value less than .05 was considered significant. Analyses were performed using SPSS version 11.0 software for Windows (SPSS, Inc, Chicago, IL).

Table 1. Characteristics of Subjects Investigated

Variable	Mean ± SD or Median (interquartile range)
Age (yr)	30.5 ± 3.5
Weight (kg)	76.2 ± 11.2
BMI (kg/m^2)	24.1 ± 3.5
Waist circumference (cm)	86.8 ± 9.9
Waist-to-hip ratio	0.9 ± 0.1
Legs fat (kg)	5.1 ± 2.0
Trunk fat (kg)	7.0 ± 4.0
Total fat (kg)	14.9 ± 6.7
Total cholesterol (mmol/L)	4.8 ± 1.2
LDL-cholesterol (mmol/L)	2.9 ± 1.0
HDL-cholesterol (mmol/L)	1.5 ± 0.3
Triglycerides (mmol/L)*	0.8 (0.6–1.1)
Fasting glucose (mmol/L)	4.2 ± 0.6
Fasting insulin (mU/L)*	7.5 (5.8–9.8)
FIRI (mmol $\times$ mU $\times$ L^{-2})*	1.3 (1.0–1.8)
Systolic BP (mm Hg)	129.5 ± 14.6
Diastolic BP (mm Hg)	80.8 ± 7.5
CRP (mg/L)*	0.65 (0.25–1.02)
IL-6 (pg/mL)*	3.12 (1.81–8.83)
Fibrinogen (mg/dL)	295.3 ± 54.5

NOTE. Variables are presented as mean ± SD, or *as median (interquartile range) for skewed variables.

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FIRI, fasting insulin resistance index; IL-6, interleukin-6; BP, blood pressure; CRP, C=reactive protein.

RESULTS

A total of 113 men were selected for the study. Twenty-six men were not enrolled (11 men were current smokers, 14 subjects had BMI $>$ 30 kg/m^2, and 1 subject used nonsteroidal anti inflammatory drug). Eighty-seven subjects who fulfilled the inclusion criteria gave their informed consent to participation. Characteristics of the population are shown in Table 1. Mean age was 30.5 ± 3.5 years. BMI ranged from 17 to 28.8 kg/m^2 and 21 subjects were overweight (BMI $>$ 25 kg/m^2). Systolic and diastolic BP values exceeding the upper normal limit ($\geq$130/85 mm Hg)[37] were found in 21 and 17 subjects, respectively; 13 subjects had elevation of both systolic and diastolic values. Eleven subjects (12.6%) had hypertension, according to international guidelines (BP $\geq$ 140/90 mm Hg).[52] Mean fibrinogen value was 295 mg/dL (interquartile range, 256 to 336); median hs-CRP level was 0.65 mg/L (interquartile range, 0.25 to 1.02) and none of the subjects had values exceeding 10 mg/L, which is the cut point usually identifying significant clinical inflammation.[24] In univariate analysis, both fibrinogen and hs-CRP levels were strongly associated with body fat content and almost all of the metabolic variables investigated (Table 2). Results of multiple regression analysis are shown in Table 3: only total body fat and LDL-C were independent predictors of fibrinogen levels, accounting for, respectively, 29.5% and 10.9% of its variance, whereas total body fat was the best predictor of hs-CRP levels, accounting for 32.5% of its variance.

Table 2. Univariate Linear Regression Analysis Between Fibrinogen, CRP, Body Fat, and Metabolic Variables in the Subjects Investigated

Variables	Fibrinogen (mg/dL)			CRP*		
	β	SE	*P*	β	SE	*P*
Legs fat (kg)	13.54	2.69	<.0001	0.25	0.048	<.0001
Trunk fat (kg)	7.33	1.34	<.0001	0.138	0.024	<.0001
Total body fat (kg)	4.429	0.80	<.0001	0.084	0.014	<.0001
Age (yr)	1.79	0.48	<.0001	0.028	0.009	0.002
Weight (kg)	1.59	0.54	0.004	0.038	0.009	<.0001
BMI (kg/m^2)	6.36	1.66	<.0001	0.147	0.028	<.0001
Waist circumference (cm)	2.73	0.56	<.0001	0.061	0.009	<.0001
Waist-to-hip ratio	347.11	91.03	<.0001	7.454	1.587	<.0001
Total cholesterol (mmol/L)	21.05	4.69	<.0001	0.139	0.094	NS
LDL-cholesterol (mmol/L)	27.45	5.36	<.0001	0.232	0.109	.037
HDL-cholesterol (mmol/L)	−15.64	18.77	NS	−0.879	0.323	.008
Triglycerides (mmol/L)*	36.72	13.94	.01	0.530	0.255	.041
Fasting glucose (mmol/L)	42.48	9.52	<.0001	0.346	0.189	NS
Fasting insulin (mU/L)*	54.77	14.87	<.0001	0.834	0.275	.003
FIRI ($mmol \times mU \times L^{-2}$)	61.03	12.61	<.0001	0.800	0.243	.002
Systolic BP (mm Hg)	1.41	0.41	.001	0.024	0.007	.001
Diastolic BP (mm Hg)	1.04	0.84	NS	0.019	0.015	NS
CRP (mg/L)*	31.29	5.38	<.0001	—	—	—
IL-6 (pg/mL)*	26.14	6.906	<.0001	0.717	0.083	<.0001

*Data logarithmically transformed.
Abbreviation: NS, not significant.

DISCUSSION

For decades, hyperfibrinogenemia has been recognized as a major risk factor for future cardiovascular events. Although several studies have clearly demonstrated strong associations of fibrinogen with most cardiovascular risk factors (age, obesity, cigarette smoking, diabetes, hypertension, dyslipidemias),[5,18,19,21-23,25,42] it is not clear which is the metabolic background accounting for the association between fibrinogen levels and cardiovascular events in healthy, non-obese, non-smoking subjects. Results of the present study show that in healthy subjects, body fat content and, marginally, LDL-C levels are the best predictors of fibrinogen levels, accounting together for more than 40% of its variance. Our findings support to the view that there is a sort of continuous relation between body fat content and fibrinogen levels, which is evident even in non-obese subjects. Beyond genetic and environmental factors, the synthesis of fibrinogen is largely regulated by IL-6.[39-42] Adipose tissue is an important source of circulating IL-6, which is elevated in obese individuals and closely related to the amount of total body fat mass.[28,35,49,50,53,54] In agreement with other studies,[13,15,18,27-30,55-58] we found that both fibrinogen and hs-CRP levels were strongly associated with almost all of the metabolic variables investigated. This evidence of a positive association between body fat, metabolic abnormalities, and acute-phase reactants levels supports the hypothesis that adipose tissue might be a common antecedent of both low-level inflammatory state and metabolic abnormalities, although the causal link between the 2 latter phenomena has not been clearly established. Therefore, fibrinogen levels, as well as hs-CRP levels, might be regarded as sensitive and composite indicators of the metabolic abnormalities associated with body fat content, thereby justifying their capacity to improve cardiovascular risk prediction based on the assessment of traditional risk factors.

Table 3. Independent Predictors of Fibrinogen and CRP Levels: Results of Multiple Regression Analyses

Dependent Variable	Independent Variables	R^2 (%)	*P*
Fibrinogen	Total body fat	29.5	<.0001
	LDL-cholesterol	10.9	<.01
	(Model)	40.4	
ln CRP	Total body fat	32.5	<.0001

Although body fat is the main predictor of both fibrinogen and hs-CRP levels, LDL-C marginally contributes to prediction of fibrinogen concentrations, but not of hs-CRP levels, which have been reported to be poorly related to T-Chol and LDL-C levels.[32] Several studies investigated the association between LDL-C and plasma fibrinogen concentration, with conflicting evidence.[13,15,18,55-58] Moreover, it has been shown that lipid-lowering therapy with some fibrates,[59,60] but not with statins,[61-63] may produce significant reductions in fibrinogen levels, despite modest decrease in LDL-C concentrations.

Results of the present study should be interpreted cautiously. Although a variable may prove to be highly significantly predictive, but not be etiologically involved, there is strong biological evidence supporting the role of adipose tissue in regulating the synthesis of acute-phase reactants.[27,28,38,40,41]

Moreover, some further limitations of the present study must be discussed. The cross-sectional design of this investigation actually does not allow a prospective evaluation of these associations, which will be addressed in future studies. Although the small size of the sample investigated might be questionable, the consistency of findings, the absence of confounding variables (such as age and smoking), and the power of associations leave little uncertainty about the possibility that different re-

sults may be observed in a larger sample of subjects. The identification of these associations within a sample of non-obese subjects may be particularly interesting because it is consistent with similar observations in obese subjects.[27-30,36] In addition, our findings suggest that also in such a low-risk population fibrinogen levels, as well as hs-CRP levels, might be regarded as sensitive and composite indicators of the initial metabolic disorder associated with body fat content. However, whether these findings on fibrinogen may add to the well-defined role of hs-CRP levels in the prediction of future cardiovascular events will need to be specifically addressed by further investigation on a larger number of subjects.

In conclusion, the results of the present study suggest that in healthy non-obese men fibrinogen concentrations, as well as CRP levels, are mainly predicted by body fat content. These findings support the hypothesis that there is a direct mechanism by which adipose tissue might regulate the levels of circulating acute-phase reactants. Assuming that both fibrinogen concentrations and CRP levels reflect future risk of cardiovascular disease,[2,3,5,13] it seems plausible to speculate that both acute-phase reactants may act as sensitive and composite indicators of the initial metabolic disorder associated with body fat content. It has been shown that both physical activity[64] and weight loss[30] may reduce levels of circulating inflammatory markers. Taken together, these findings would suggest that dietary and physical approaches to avoid obesity might be beneficial in reducing circulating levels of acute-phase reactants and future cardiovascular risk.

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